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**Active, personalized, and balanced coagulation management saves lives in  
patients with massive bleeding**

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**Editorial View on the following review article:** Pathophysiology and Treatment of Coagulopathy in Massive Hemorrhage and Hemodilution. Daniel Bolliger, MD, Klaus Görlinger, MD, Kenichi A. Tanaka, MD MSc

**Title of the Editorial View (MS # ALN201006083):** Active, personalized and balanced coagulation management saves lives in massive bleeding patients

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**Editorial View:**

Massive hemorrhage originates from severe injury of blood vessels caused by major trauma or surgery, an underlying medical condition, or any combination thereof. If not diagnosed and treated readily, patients exsanguinate and die from hypovolemic shock. In this issue of ANESTHESIOLOGY, *Bolliger et al.*<sup>1</sup> review the mechanisms of coagulopathy in massive hemorrhage with a special emphasis on hemodilutional effects of fluid therapy on thrombin generation, fibrin polymerization and fibrinolysis. A proper understanding of the complex pathophysiology of coagulopathy in massive bleeding patients is essential for effective treatment. The coagulation system represents a delicate balance between pro- and anti-coagulant as well as pro- and anti-fibrinolytic protein activities. Modern coagulation management of bleeding patients implies an ongoing monitoring of the coagulation status with subsequent individual and goal-directed treatment. The key to success in terms of patient outcome is to keep the above mentioned four elements of the coagulation system in an optimal equilibrium so that bleeding is adequately controlled without thromboembolic adverse events.<sup>2</sup>

The coagulation system is a complex network of interacting proteins and cells with extensive sensitivity, amplification and control pathways. For any given patient, there is no simple answer to coagulation management, but instead, optimal coagulation intervention and management needs to be defined for each patient.<sup>3</sup>

Advanced coagulation monitoring will employ a combination of routine laboratory coagulation tests, single factor measurements and whole blood, point of care coagulation testing, always keeping in mind the patient's history and clinical findings.<sup>4</sup> Whole blood coagulation tests like Thrombelastography® (Haemonetics Corporation, Braintree, MA) or rotation Thromboelastometry® (Tem International

GmbH, Munich, Germany) may overcome some of the limitations of routine laboratory coagulation tests and are increasingly being used in massive bleeding patients. With minimal time delays, they provide valuable information on overall kinetics of clot formation, clot strength, platelet function and overt fibrinolysis in whole blood.<sup>5</sup> However, these tests are still *in vitro* assays; they do not reflect *in vivo* contributions of local tissue and the endothelium, tissue factor bearing cells, and blood flow to the naturally occurring coagulation process. Therefore, any coagulation test requires skilled interpretation and clinical correlation in evaluating its significance for bleeding or thrombosis.

Patients with massive hemorrhage become coagulopathic due to several mechanisms. Trauma and shock directly activate the thrombomodulin-protein C pathway resulting in the acute coagulopathy of trauma and shock.<sup>6-8</sup> Thereby, key players of the propagation phase of coagulation, the tenase (VIIIa-IXa) and prothrombinase (Xa-Va) complex are getting degraded and inactivated by activated protein C. Furthermore, plasminogen activator inhibitor 1, the principal inhibitor of tissue plasminogen activator and urokinase, activators of plasminogen and hence fibrinolysis is consumed through activated protein C, resulting in increased fibrinolysis. The developing coagulopathy then gets worse through the better known pathogenetic factors: consumption and dilution of coagulation factors, hypothermia and acidosis.

Fibrinogen is the substrate of coagulation and is usually the first coagulation factor to become critically low in massive bleeding.<sup>2</sup> According to *Hiippala et al.*,<sup>9</sup> fibrinogen levels fall below 1 g/L after a loss of 150% of the calculated blood volume. Factor II, V, VII and platelet levels become critical later, after a loss of >200% of the blood volume. However, these figures are very general and do not help greatly in the

individual case. In addition, the arbitrary definition of the critical level determines when the corresponding level will be reached i.e. after what blood volume loss.

If patients present with clinical and objective signs of coagulopathic bleeding, treatment with allogeneic blood products (fresh frozen plasma, cryoprecipitate, platelet concentrates), factor concentrates, pharmacological interventions or a combination thereof has to be initiated. Evidence-based recommendations, like the one from the multidisciplinary Task Force for Advanced bleeding Care in Trauma,<sup>2</sup> updated in 2010 are very helpful for optimal patient care. One request of the review by *Bolliger et al.*<sup>1</sup> is that the efficacy and safety of novel hemostatic therapies like factors concentrates are to be assessed in clinical studies. This is certainly correct, but this also applies for the traditional use of fresh frozen plasma, cryoprecipitate and platelets.

Transfusion of allogeneic blood products is independently associated with increased mortality and major adverse cardiac and non-cardiac outcomes.<sup>10</sup> One strategy to reduce bleeding and avoid allogeneic blood transfusion in surgical patients at increased risk of bleeding is the use of anti-fibrinolytics. For almost two decades, published literature demonstrated the relative safety and efficacy of aprotinin, a nonspecific serine protease inhibitor especially in adult cardiac surgical patients at increased risk of bleeding. However, since the Blood Conservation Using Anti-fibrinolytics in a Randomized Trial<sup>11</sup> has been published in 2007, aprotinin has been withdrawn from the market. The Blood Conservation Using Anti-fibrinolytics in a Randomized Trial represented the largest prospective, randomized, blinded head-to-head comparison of 3 major anti-fibrinolytic agents in current clinical usage.<sup>12</sup> The study was terminated early because of a trend towards higher mortality in patients treated with aprotinin.<sup>11,12</sup>

Since marketing of aprotinin has been suspended, only two anti-fibrinolytics remained commercially available in the United States and European Union for patient use, i.e.  $\epsilon$ -aminocaproic acid and tranexamic acid (TXA). Both drugs are lysine analogues and inhibit fibrinolysis by competitively blocking the lysine binding site on plasminogen.<sup>13</sup> Lysine analogues have shown to reduce blood loss and the need for allogeneic red cell transfusion, especially in cardiac, liver and orthopedic surgery. The lysine analogues (evidence is stronger for TXA than for  $\epsilon$ -aminocaproic acid) were probably as effective as aprotinin in most studies but at lower costs.<sup>14</sup> The results of a cutting-edge landmark trial on the use of TXA in trauma patients, the CRASH-2 trial (NCT00375258) have just been published.<sup>15</sup>

CRASH-2 is a multicenter (274 hospitals in 40 countries), randomized, blinded and placebo controlled trial on the effects of TXA administration on death, vascular occlusive events, surgical interventions and blood transfusion in 20,211 adult trauma patients.<sup>15</sup> Within 8 h of injury, patients with significant hemorrhage, or who were considered to be at risk of significant hemorrhage, received either 2 g TXA (1 g loading dose, followed by a maintenance dose of 1 g over 8 h) or placebo. TXA administration reduced all-cause mortality (14.5 vs. 16.0%; relative risk 0.91, 95% CI 0.85-0.97;  $p=0.0035$ ) and the risk of death from hemorrhage (4.9% vs. 5.7%; relative risk 0.85, 95% CI 0.76-0.96;  $p=0.0077$ ) without an increase in fatal or non-fatal vascular occlusive events, e.g. stroke, myocardial infarction, deep vein thrombosis or pulmonary embolism. Surprisingly however, there was no statistical difference in blood transfusion between the groups. The question on how TXA reduced the risk of death in bleeding patients remains unanswered by the CRASH-2 study and it may be speculated that TXA might have additional, beneficial effects on patient outcome beyond simply inhibiting fibrinolysis.<sup>16</sup> Another large-scale prospective, randomized, double blind, placebo controlled trial on the use of anti-fibrinolytics is planning to

enroll 15,000 women with a clinical diagnosis of postpartum hemorrhage (WOMAN trial; NCT00872469).<sup>17</sup> Data should be available after completion in 2015.

How should all these aspects translate into perioperative, hemostatic management? *First*, we have to thoroughly understand the pathophysiology of the deranged coagulation system in massive bleeding, and in particular understanding that blood coagulation does not only consist of pro-coagulant proteins. We always have to consider the four elements of the coagulation system and keep them in balance, i.e. pro- and anti-coagulant as well as pro- and anti-fibrinolytic 'sub-systems'. *Second*, we have to carefully diagnose the main problem of the disturbed coagulation system with patient's history, clinical findings and adequate blood tests. Since blood coagulation may change rapidly during massive hemorrhage, frequent re-assessment is necessary. Furthermore, we need to exactly know how to interpret the blood tests ordered, what they can tell us and where their limitations are. *Third*, we are to initiate the specific treatment needed by the individual patient early. The review by *Bolliger et al.*<sup>1</sup> is an important contribution toward better understanding of coagulopathy in massive hemorrhage and hemodilution. The better we know the underlying pathophysiology, the better we can diagnose and treat our patients targeted to their individual needs.

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